## REMARKS

Accordingly, claims 2, 4-9, 16-46, 47-54, 64-74, 76-105 were pending in the application. Claims 64-74 and 76-90 have been canceled as being directed to non-elected subject matter. Claims 51, 52 and 92 have been canceled. Claims 15, 16, 47, 48, 54, 9193, 97 and 105 have been amended. Accordingly, after the amendments herein have been entered, claims 2, 4-9, 14-16, 47-50, 53-54, 91 and 93-105 will remain pending.

*No new matter has been added.* Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

***Objections to the Specification***

The Examiner has made a number of objections to the specification and abstract. Applicants have amended the abstract to remove legal phraseology. Applicant have also amended the specification to remove typographical errors, thereby rendering these objections moot.

The Examiner has also questioned whether the large blank space on page 34 was left there intentionally. Applicants confirm that the majority of page 34 was intentionally left blank.

***Objections to the Claims***

The Examiner has objected to a number of claims for typographical or grammatical errors. These claims have been amended, thereby rendering these objections moot.

The Examiner has also objects to claims 51 and 52 as being substantial duplicates of claim 48. Applicants have canceled claims 51 and 52 thereby rendering this rejection moot.

Applicants respectfully request that the Examiner reconsider and withdraw these objections.

***Rejection of Claims 48-54 Under 35 USC 112, First Paragraph***

The Examiner has rejected claims 48-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner believes that

> [t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
>
> The claims are specifically drawn to a "pharmaceutical composition" comprising an antisense compound comprising SEQ ID NO:8 further comprising nucleotide analogues. The preamble language `"pharmaceutical" reflects that the antisense compound comprising SEQ ID NO:8 must confer pharmaceutical or therapeutic effects *in vivo*.

Applicants respectfully traverse this rejection.

The Examiner cites Patil et al. as art evidencing the lack of a correlation between in vitro and in vivo activity of DNA therapeutics. However, Patil et al.'s conclusions on DNA based drugs do not apply to the claimed compositions since the claimed compositions contain nucleotide analogues. In fact, Patil et al. come to the same conclusion on page E62, column 1, last sentence: *"Chemical derivatization has yielded excellent results for improving the biological stability of short-length DNA-based therapeutics such as oligonucleotides".*

Therefore, the Patil et al. does not support the Examiner's enablement rejection.

The Examiner further contends that it would constitute an undue burden on one of skill in the art to establish whether the claimed compositions have an effect *in vivo* since "neither antisense therapeutics nor clinical trials are performed routinely in the art". On the other hand, the Examiner emphasises that Example 17 discloses enabled *in vivo* results for compounds of SEQ ID NO:14A.

Therefore, if the Examiner considers the *in vivo* effect as enabled for SEQ ID NO:14A, it would only require routine experimentation for one of skill in the art to apply the procedure of Example 17 to compositions comprising compounds of SEQ ID NO:8 to establish whether they have *in vivo* activity in addition to the demonstrated *in vitro* activity. Accordingly, the required experimentation would not constitute an undue burden to the person skilled in the art.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the forgoing rejection.

***Rejection of Claims 2, 5-9, 15-16, 48-54, and 91-105 Under 35 U.S.C. 112, First Paragraph***

The Examiner has rejected claims 2, 5-9, 15-16, 48-54, and 91-105 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner is of the opinion that

> the breadth of the instantly claimed invention embraces any species of nucleic acid compounds such as antisense oligonucleotides, siRNAs, ribozymes, DNAzymes, aptamers, and so forth, as evidenced by the broad definition of the

term "oligomeric compound" provided on page 11 of the instant specification. As broadly claimed, the specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed in the instant claims because it discloses that the inventors were in possession of no other species of oligonucleotides than LNA antisense oligonucleotides at the time of the instant tiling date. Since antisense oligonucleotides disclosed therein are not representative of the genus of nucleic acid compounds (or oligomeric compounds) encompassed by the broadly' recited claims, one of ordinary skill in the art cannot recognize what is claimed in claims 2, 5-9, 15-16, 48-54, and 91-105.

Applicants respectfully traverse this rejection. However, while in no way acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting prosecution, Applicant have amended claim 91 to indicate that the nucleotide analogue is an LNA sugar, 2'-O-methyl-RNA sugar, 2'-fluoro-DNA sugar, 2'-MOE-RNA sugar, 2'-O-(3-amino)propyl-RNA sugar or 2'-O-(3-hydroxy)propyl-RNA sugar. It is known in the art and clear to the skilled artisan based on the application as filed how to make these analogues. Applicants have further amended claim 91 to indicate that the compounds claimed are antisense oligonucleotides.

Accordingly, Applicants respectfully set forth that the claims are fully described in the specification as filed and respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

***Rejection of Claims 2, 4-9, 14-16, 47-54, and 91-105 Under 35 U.S.C. 112, Second Paragraph***

Claims 2, 4-9, 14-16, 47-54, and 91-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have amended or canceled these claims to overcome the 35 USC 112, second paragraph issues.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

***Rejection of Claims 2, 4-5, 9, 15, 48-54, and 91 Under 35 U.S.C. 102(b)***

The Examiner has rejected claims 2, 4-5, 9, 15, 48-54, and 91 under 35 U.S.C. 102(b) as being anticipated by Wright et al. (WO 99/38963). Specifically, the Examiner believes that

> [t]he claims are drawn to an antisense compound consisting of 12-50 nucleotides, wherein at least 8 nucleotides are located within the SEQ ID NO:8, comprising nucleotide analogues at different nucleotide positions, wherein the antisense compound is incorporated into a pharmaceutical composition further comprising a pharmaceutically acceptable carrier or salt thereof and further comprising a chemotherapeutic agent.
>
> And further,
>
> Given the broadest reasonable interpretation of the claim, claim 91 reads on any nucleic acid compound comprising any nucleotides selected from those of SEQ ID NO:8 in any sequential order. That is, the instantly claimed invention reads on any nucleic acid compound comprising at least 8 of "C", "A", "G", and "T" set forth in SEQ ID NO:8, which make up to be 12-50 nucleotides in order to fulfill the structural requirements set forth within claim 91. In other words, there is no requirement that the recited "subsequence" must be arranged in a consecutive or contiguous manner.
>
> Wright et al. teach a number of different antisense compounds of 17 to 20 nucleotides in length, which are targeted to thioredoxin mRNA sequence as is the case with the instant application. See Table 1. Each of the 26 antisense oligonucleotide sequences set forth in Table 1 comprises at least 8 nucleotides of SEQ ID NO:8 consisting of "CAAGGAATATCACGTT".

Applicants traverse this rejection. For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

The claims have been amended to be directed to a compound consisting of a total of 12-50 nucleotides and/or nucleotide analogues, wherein said compound comprises a subsequence of at least 8 nucleotides or nucleotide analogues, said ***subsequence comprising at least an 8-nucleobase portion*** of the sequence caaggaatatcacgtt, i.e., a contiguous 8-nucleobase portion.

Accordingly, Wright et al. does not teach each and every element of the instant claims. Accordingly, the instant claims are novel over the teachings of Wright et al. Applicants respectfully request the reconsideration and withdrawal of the foregoing rejection.

***Rejection of Claims 2, 4-9, 14-16, 51-54, and 91-97 Under 35 U.S.C. 103(a)***

The Examiner has rejected claims 2, 4-9, 14-16, 51-54, and 91-97 under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (WO 99/38963) in view of Thrue et al. (US 2004/0096848 Al). Specifically, the Examiner believes that

> Thrue et al. teach that the LNA analogue is most preferred as the choice of nucleotide analogue substitutions because it displays the ability to penetrate a cell membrane, good resistance to extra- and intracellular nucleases, high affinity and specificity for the nucleic acid target (paragraph 0032). They further teach that beta-D-oxy-LNA is a superb form of nucleotide analogue because it exhibits unprecedented binding properties towards DNA and RNA target sequences (paragraph 0083). They teach that gapmers are chimeric oligonucleotides composed of beta-D-oxy-LNA and DNA, wherein DNA sequence is flanked by 1 to 6 residues of beta-D-oxy-I,NA (paragraph 0096). They also teach that the LNA can be 5' methyl cytosine (paragraph 0056).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the thioredoxin oligonucleotides of Wright et al. in view of Thrue et al. One of ordinary skill in the art would have been motivated to combine the teachings of Wright et al. and Thrue et al. in order to make an effective thioredoxin antisense oligonucleotide compound that displays high affinity and specificity for the thioredoxin target sequence thereby resulting in an efficacious reduction of tumor growth *in vitro* or *in vivo*.

Applicants respectfully traverse this rejection. As indicated above, Wright et al. do not teach or suggest the compounds set forth in the instant invention. Moreover, Thrue et al. does not make up for the deficiencies of Wright et al. Therefore, the combination of Wright et al. and Thrue et al. would not lead one of skill in the art to the claimed invention.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

## CONCLUSION

In view of the above amendment, Applicants believe that the pending application is in condition for allowance. If a telephonic conversation would be helpful, the Examiner is urged to contact the undersigned.

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Respectfully submitted,

By _____

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